PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WO/175	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/EP2004/052201	International filing date *(day/month/year)* 16.09.2004	Priority date *(day/month/year)* 25.09.2003
International Patent Classification (IPC) or national classification and IPC C07C257/14, C07C309/66, C07D233/10, C07D273/04, C07D211/26, C07D333/24, A61K31/155, A61K31/255, A61K31/381, A61K31/4164, A61K31/4453, A61K31/5395, A61P17/06		
Applicant DOMPE S.P.A. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 5 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) ., containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.07.2005	14.09.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/052201

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-17 as originally filed

   Claims, Numbers

   1-11 received on 22.07.2005 with letter of 22.07.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/052201

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Section V.

1). No compounds of the formulae given in claims 1 and 2 could be found in the prior art. The subject-matter of claims 1-6,10 and 11 is novel.

2). No disclosure of the use of the compounds given in claim 7 could be found in the prior art. The subject-matter of claims 7-9 is also novel.

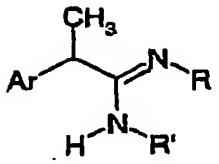
3). The object of the present application is to provide new compounds inhibiting IL-8 induced polymorphonucleated neutrophils which are as such of interest in the treatment of the diseases noted in claim 9. The compounds for which this use is claimed and the compounds claimed as such differ from the compounds of WO-A-0 158 852, (D13), which also have this property, at least in the replacement of the amide carbonyl by the C=N-R moiety. In view of this structural difference, it could not be expected that the presently specified compounds would also have the utility noted in claim 9. Claims 1-9 are therefore based on an inventive step and claims 10 and 11 are inventive by analogy.

Section VIII.

Some of the compounds according to claim 2 are no longer dependent on claim 1. These should be made the object of a separate independent claim.

CLAIMS

1. Amidines of formula (I)



(I)

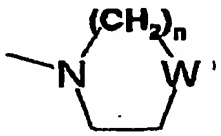
and pharmaceutically acceptable salts thereof,

wherein Ar is selected from:

3'-benzoylphenyl, 3'-(4-chloro-benzoyl)-phenyl, 3'-(4-methyl-benzoyl)-phenyl, 3'-acetyl-phenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxyphenyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'acetylamino-phenyl, 4'propionylamino-phenyl, 4'-benzoylamino-phenyl;

R is selected from

- H, C_1-C_5-alkyl, phenyl, C_1-C_5-phenyalkyl, C_1-C_5-cycloalkyl, C_1-C_5-alkenyl, C_1-C_5-alkoxy;
- a residue of formula $-(CH_2)n$-NRaRb wherein n is an integer from 0 to 5 and each Ra and Rb, which may be the same or different, are C_1-C_6-alkyl, C_1-C_6-alkenyl or, alternatively, Ra and Rb, together with the nitrogen atom to which they are bound, form a heterocycle from 3 to 7 members of formula (II),



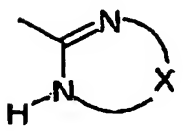
(II)

wherein W represents a single bond, O, S, N-Rc, Rc being H, C_1-C_6-alkyl or C_1-C_6-alkylphenyl.

R' is H, CH_3, CH_2CH_3;

R and R' can alternatively, form a heterocycle from 5 to 7 members of formula (III),

2



(III)

wherein X represents a residue $-O(CH_2)n-$ wherein n is an integer from 1 to 3, or a residue $-(CH_2)n-$ wherein n is an integer from 2 to 4, or the ethylene residue –CH=CH-.

2. Compounds according to claim 1 selected from:

(R,S) (2-(4-isobutylphenyl)propionamidine hydrochloride

(+) (2-(4-isobutylphenyl)propionamidine hydrochloride

(-) (2-(4-isobutylphenyl)propionamidine hydrochloride

(R,S) 2-(3-benzoylphenyl)propionamidine hydrochloride

(R,S) 2-[(3-fluoro-4-phenyl)phenyl]propionamidine hydrochloride

(R,S) 2-(4-trifluoromethanesulfonyloxyphenyl)propionamidine hydrochloride

(R,S) 2-(5-benzoyl-2-thiophene)propionamidine hydrochloride

(R,S) 2-(4-isobutylphenyl)-N-[3"-(N'-piperidino)propyl]propionamidine dihydrochloride

(R,S) 2-(4-isobutylphenyl)-N-methyl-propionamidine hydrochloride

(R,S) 2-(3-benzoylphenyl)- N-[3-(N,N-dimethylamino)propyl]propionamidine hydrochloride

(R,S) 2-(4-isobutylphenyl)propionamidine acetate salt

(R,S) 2-(4-isobutylphenyl)-N-[3-(N,N-dimethylamino)propyl] propionamidine

(R,S) 2-(4-isobutylphenyl)-N-benzyl propionamidine

(R,S) 3-[1-(4-isobutylphenyl)ethyl]-5,6-dihydro-2H-1,2,4-oxadiazine

(R,S) 2-[1-(4-isobutylphenyl)ethyl]-4,5-dihydro-2H-1,3,imidazole.

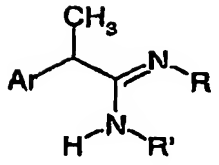
3. Compounds according to claims 1 or 2, for use as medicaments.

4. Use of compounds according to claims 1 or 2 in the preparation of a medicament for the treatment of diseases that involve the chemotaxis of human PMNs induced by interleukin-8.

5. Use of compounds according to claims 1 or 2 in the preparation of a medicament for the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigo, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.

6. Pharmaceutical compositions comprising a compound according to claims 1 or 2 in admixture and a suitable carrier thereof.

7. Use of amidines of formula (I)



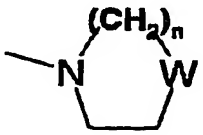
(I)

and pharmaceutically acceptable salts thereof,

wherein Ar is a phenyl group non-substituted or substituted by one or more groups independently selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halogen-C_1-C_3-alkyl, halogen C_1-C_3-alkoxy, benzoyl or a substituted or unsubstituted 5-6 membered heteroaryl ring selected from pyridine, pyrrole, tiofene, furane, indole.

R is selected from

- H, C_1-C_5-alkyl, phenyl, C_1-C_5-phenyalkyl, C_1-C_5-cycloalkyl, C_1-C_5-alkenyl, C_1-C_5-alkoxy;
- a residue of formula $-(CH_2)n$-NRaRb wherein n is an integer from 0 to 5 and each Ra and Rb, which may be the same or different, are C_1-C_6-alkyl, C_1-C_6-alkenyl or, alternatively, Ra and Rb, together with the nitrogen atom to which they are bound, form a heterocycle from 3 to 7 members of formula (II),

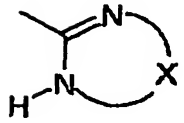


(II)

wherein W represents a single bond, O, S, N-Rc, Rc being H, C_1-C_6-alkyl or C_1-C_6-alkylphenyl.

R' is H, CH_3, CH_2CH_3.

R and R' can alternatively, form a heterocycle from 5 to 7 members of formula (III),



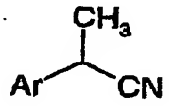
(III)

wherein X represents a residue $-O(CH_2)n-$ wherein n is an integer from 1 to 3, or a residue $-(CH_2)n-$ wherein n is an integer from 2 to 4, or the ethylene residue –CH=CH- in the preparation of a medicament for the treatment of diseases that involve the chemotaxis of human PMNs induced by interleukin-8.

8. Use of compounds according to claim 7, wherein R is selected from
- hydrogen
- a residue of formula $-(CH_2)_n-NRaRb$, wherein n is an integer from 2 to 3 and the group NraRb is selected from N,N-dimethylamine or 1-piperidyl, and R' is H, or R and R' form a heterocycle of formula (III), where X represents a residue $-O(CH_2)n-$ wherein n is the integer 1 or 2, or a residue $-(CH_2)_2$.

9. Use of compounds according to claims 7 or 8 in the preparation of a medicament for the treatment of psoriasis, ulcerative colitis, melanoma, chronic obstructive pulmonary disease (COPD), bullous pemphigo, rheumatoid arthritis, idiopathic fibrosis, glomerulonephritis and in the prevention and treatment of damages caused by ischemia and reperfusion.

10. Process for the preparation of compounds of formula (I) according to claim 1 comprising the reaction of a nitrile derivate of formula (IV),



(IV)

wherein Ar has the same meaning as defined in claim 1, with an amine of formula NHR, wherein R has the same meaning as defined in claim 1.

11. Process for the preparation of compounds of formula (I) according to claim 1, wherein R and R' groups form an heterocycle of formula (III), comprising the reaction of amidines of formula (I) wherein R' is H and R is H or OH, with a reagent of formula L-K-L', in the presence of a base, wherein L and L' are leaving groups, and, when R and R' are both H, K

represents a residue -(CH_2)n- wherein n is an integer from 2 to 4; when R is OH and R' is H, K represents a residue -(CH_2)n- wherein n is an integer from 1 to 3.